EXHIBIT A

Risk of Cancer with Exposure to NDMA: An Analysis of Epidemiologic Data

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EXECUTIVE SUMMARY

This report examines whether N-Nitrosodimethylamine also referred to **NDMA** or N-Nitrosodiethylamine also referred to as **NDEA,** both present in excessive amounts in some manufactured batches of the drug **valsartan**, can increase the risk of different types of cancer. To answer this question, I conducted a systematic search of the scientific evidence and systematically appraised the available evidence on the risk of NDMA and cancer, with a focus on the strength of the evidence from epidemiological data. Data from large epidemiologic studies that examined NDMA exposure (from both occupational and dietary sources) with respect to different types of cancer formation or cancer deaths are discussed. Studies that attempt to specifically examine the risk of cancer from NDMA and NDEA containing valsartan are also examined. I apply the Bradford Hill criteria and the evidence ascertained in my search demonstrate a causal link between exposure to NDMA and NDEA contained in valsartan and the following types of cancers: **esophageal, stomach, colorectal, liver, pancreas, lung, bladder, prostate and blood (leukemia, lymphoma and multiple myeloma**).

1.0 QUALIFICATIONS

1.1 Education

I am currently an Associate Professor of Ophthalmology and Visual Sciences and an Associate Member at the Departments of Medicine and Pharmacology. I received a bachelor's degree (BSc) in Pharmacy from the University of British Columbia in 1995. After working as a pharmacist for seven years, I returned to school and earned a Doctor of Pharmacy degree from Idaho State University. The doctoral program was a two-year advanced post-graduate degree in clinical pharmacology that involved direct patient contact and close collaborative relationships with physicians aimed at optimizing patient drug therapy regiments.

In 2003, I completed a master's degree (MSc) in Clinical Epidemiology at the University of Toronto. I held a Post-Doctoral Fellowship and continued my training in Pharmacoepidemiology and Drug Safety at McGill University. In 2019, I was awarded the distinguished achievement award in clinical research from the UBC Faculty of Medicine.

1.2 Training

My training spans the fields of both pharmacology and epidemiology. Specifically, I have familiarity in the disciplines listed below although my areas of expertise and research are focused on epidemiology, pharmacoepidemiology and causal inference (causation in epidemiology).

- **Basic Pharmacology**: The study of drug mechanisms of action in animals or humans. Pharmacology focuses on the action of drugs at the molecular level and hence is considered a 'basic' science.
- **Clinical Pharmacology**: The study of drug action in the human body. Clinical Pharmacology addresses the clinical effects of drugs specifically in the areas of: 1) drug dosing; 2) drug efficacy and or effectiveness; and 3) monitoring and assessing adverse drug events.
- **Clinical Pharmacokinetics:** This area of pharmacology examines mechanisms of drug absorption, distribution, metabolism, and excretion in the human body.
- **Drug Interactions:** The study of identifying and managing adverse events that occur with co-administration between two distinct drugs.
- **Pharmacoepidemiology:** A combined discipline of epidemiology and pharmacology. Pharmacoepidemiology uses large clinical, administrative or health claims databases to study the use and effects of drugs in large populations.
- **Causal Inference in Epidemiology:** The science of causation in the area of Epidemiology and Medicine.

1.3 Drug Safety Experience

I have 20 years of experience as a clinical pharmacologist and pharmacoepidemiologist. Since 2002, I have been involved in conducting and publishing drug safety studies (also referred to as pharmacoepidemiologic studies). These studies have covered a wide range of topics related to drug effectiveness and safety in numerous therapeutic classes including non-steroidal anti-inflammatory drugs (NSAIDs), antibiotics, antipsychotics, antidepressants, antihypertensives, 5-alpha reductase inhibitors (such as Proscar®), phosphodiesterase inhibitors (such as Viagra®), testosterone therapies (such as Androgel®), hormone replacement therapy, oral contraceptives, acne medications (such as isotretinoin), osteoporosis medications (such as Fosamax®) and fluoroquinolone antibiotics such as Cipro® among others.

I have published close to 180 peer-reviewed articles on various drug safety topics in top tier journals including the *Journal of the American Medical Association (JAMA), The British Medical Journal (BMJ), the Canadian Medical Association Journal (CMAJ), JAMA Ophthalmology and Journal of the National Cancer Institute.* I am also a reviewer and consultant on drug safety manuscripts submitted for publication to the aforementioned journals and a regular reviewer for *JAMA, British Journal of Clinical Pharmacology,* and *Movement Disorders*. I have specifically published a landmark study in the *Journal of the National Cancer Institute*[1], as well as a landmark review on the risk of hair dyes and cancer in *JAMA*[2]. In addition to scientific journals, my research has also been published in prestigious mainstream media, including the *Wall Street Journal*[3] and the *New York Times*[4].

I have also acted as a consultant to drug regulatory agencies on topics related to drug safety. Recently, I was a consultant for the Food and Drug Administration (FDA), Health Canada, as well as the European Medicines Agency regarding a study we published on the use of oral fluoroquinolones (such as Cipro®, Levaquin and Avelox®) and the risk of retinal detachment. Our findings have been used by some of these agencies and led to the publication of warning letters intended to caution physicians of on this risk. In the past five years my research has also involved applying principles of causation in epidemiology (also referred to as causal inference) to drug safety studies. I have published two landmark studies in this area[5,6].

1.4 Compensation and Testimony

- My hourly billing rate is **$475/HR**.

Testimony experience, United States:

- I have given deposition testimony in the cases of, **Risperdal®** and **Invega®** products liability cases, (Superior court of the state of California, Proceeding # 4775) and **Risperdal®** (United States court for the state of Delaware, case # 14-1366-RGA)

Testimony experience, Canada:

- **Invokana®** (Canadian litigation Q.B.G. 2236 of 2016, Court of Queen's Bench of Saskatchewan)

Trial testimony experience

- I have not testified in trial in the last 4 years:

2.0 WHAT ARE NDMA AND NDEA?

NDMA (N-Nitrosodimethylamine) and NDEA (N-Nitrosodiethylamine) are both chemicals within the nitrosamine family, which is the name given to a unique class of compounds that share a unique structure containing nitrogen (N). Both NDMA and NDEA are found in industrial by-products such as pesticides and hair dye. NDMA and NDEA are also found in the air, water and food (cured meats).

3.0 NDMA/NDEA AND CARCINOGENCITY

The International Agency for Research on Cancer (IARC), the scientific body of the World Health Organization (WHO), has stated that NDMA is clearly carcinogenic[7] and the United States Environmental Agency (USEA)[8] has classified NDMA and NDEA as probable carcinogens. Animal studies, mainly with rodents, have shown that when animals were exposed to NDMA through diet or water[9,10] they developed cancer. Both NDMA and NDA have been shown to be cancer initiators[11,12]. They are both used to induce cancers in animals[11,12] by inducing cellular genotoxicity and direct chromosomal damage to the DNA[13]. NDMA has also shown be a cancer promoter[14,15].

In animals, the effect of NDMA on cellular damage has been shown with different routes of administration, including inhaled[16] and injected[17]. Similarly, NDEA has also shown to increase the risk of cancerous tumors in animals[18,19] and its daily allowable limit is even lower (1/3, 26.5ng vs 96.0) compared with NDMA suggesting its higher carcinogenic potential (FDA)[20].

4.0 VALSARTAN CONTAINING NDMA/NDEA AND CARCINOGENCITY

Valsartan is a drug also available by the brand name Diovan® (Novartis). Valsartan is a member of the drug class referred to as angiotensin receptor blockers or (ARBs). Valsartan is mainly prescribed to treat high blood pressure or heart failure, or to preserve renal function. The drug is available by itself as a single agent or in combination with other antihypertensive drugs, mainly hydrochlorothiazide (a diuretic) or amlodipine (a calcium channel blocker).

In 2018, the FDA issued a recall for some manufactured batches of generic valsartan. The FDA's actions were due to finding an excessive allowable concentration of NDMA in these lots, which was deemed higher than the daily allowable dose of 96 nanograms (ng) set by the FDA[20.] Tests performed by the FDA have shown that some lots of valsartan contained NDMA concentrations exceeding 200 times the allowable limit of 96 ng/day[21]. To provide context, the range of the amount of daily NDMA in a person's diet in the United States estimated by Hrudey[22] is at a range of 30 to 60 ng/day in adults[22].

Similarly, the daily allowable limit for NDEA set by the FDA, is 26.5 ng/day[20] which according to the FDA is 50 times lower than the NDEA[21] content in some of the valsartan formulations as alerted by the FDA and approximately 1/3 the allowable daily limit set for NDMA suggesting the higher potency of NDEA compared with NDMA[20].

The nitrosamine levels tested among different manufacturers have had variable concentrations[i].

[i]Testing result documents demonstrate ranges of NDMA and NDEA contamination. Examples of which are: ZHP ZnCl2 process tested for NDMA ranged from 3.4 to188.1 ppm and TEA process tested for NDMA ranged from ND to 73.9. (ZHP00079920-9940). TEA process tested for NDEA ranged from 0.03 to 42.14 ppm and ZnCl2 process tested for NDEA ranged from 0 to 4.23 ppm. (PRINSTON0075857-858);**Hetero:** NDMA ranged from 0.82 to 2.69 ppm. (HETERO_USA000025250-251);**Mylan:** NDMA ranged from 0.01 to 0.09 ppm. NDEA showed a range of 0.1-1.57ppm. (MYLAN-MDL2875-00895544); **Aurobindo**: NDMA ranged from 0.106 to 0.129 ppm. NDEA ranged from 0.028 to 1.508 ppm. (Auro-MDL-2875-0093561; Auro-MDL-2875-0104586);**Teva:** NDMA ranged from 0.02 to 31.3 ppm. (TEVA-MDL2875-00069442; TEVA-MDL-00693423). NDEA ranged from 0.02-0.50 ppm. (TEVA-MDL2875-00048605);**Torrent:** NDMA range from 0.37 to 125.15ppm. (TORRENT-MDL2875-00366172). NDEA range from 0.23 to 16.93ppm. (TORRENT-MDL2875-00135398)

5.0 ASSESSING THE RISK OF CANCER WITH NDMA/NDEA EXPOUSRE

The optimal approach in assessing the risk of cancer with NDMA and NDMA containing valsartan is by careful assessment of data from large population based epidemiologic studies. In order to infer whether prolonged NDMA exposure (through occupational exposure, dietary ingestion from foods or direct ingestion from valsartan tablets) can cause cancer, I reviewed both basic science and epidemiologic evidence on this topic. I then applied the Bradford Hill[23] criteria and used the available scientific evidence to decide on the presence of a causal link between NDMA or NDEA exposure and cancer.

6.0 OBJECTIVE OF EPIDEMIOLOGIC STUDIES

The strength of epidemiologic studies is that they can provide information on a specific exposure/outcome relationship in large populations. Epidemiologic studies can determine disease risk factors or quantify patterns of use of a particular intervention in a population. Another strength of epidemiologic studies is their ability to examine and quantify cause and effect relations between certain exposures (a drug or carcinogen) and diseases (cancer). These studies are at times referred to as etiologic studies and the specific area in epidemiology that addresses cause and effect is referred to as *causal inference*.

Etiologic studies usually follow epidemiologic methodology to show a causal relation between exposure A and outcome B. The objective of these types of studies is to control for as many confounders as possible. Confounders are variables that can be associated with both A and B and in doing so might distort the true presence of a casual relation between A and B. When important confounders and potential biases are controlled for and other important factors necessary for a causal relation are present (such as those stated by Bradford Hill[23]), it is possible to discern from epidemiologic studies the likelihood that exposure A can cause outcome B[24].

7.0 STUDY DESIGN AND STATISTICAL CONCEPTS USED TO ASSESS CAUSATION IN EPIDEMIOLOGY

Epidemiologic study designs that can assess causation in medicine can be divided into two main categories—randomized controlled trials (RCTs) and observational studies.

7.1 Randomized Clinical Trials (RCTs)

RCTs are considered true experiments and are studies where subjects are randomized to receive an active drug or placebo. For example, the studies that the FDA requires to establish a drug's efficacy (e.g., COVID-19 vaccines) are RCTs. The strength of RCTs is their ability to randomize subjects to the treatment, as well as blind subjects (and at times investigators) to the treatment.

Randomization ensures that each subject has an equal chance of receiving the drug or placebo, and thus both groups are balanced with respect to characteristics or variables that may affect the outcome. In contrast, consider a non-randomized study investigating whether a blood pressure-lowering medication can lower the risk of heart attack. Investigators might find, for example, that subjects taking the medication are at a *higher* risk of developing heart attacks. One possible

explanation could be that those taking the medications had a higher cardiovascular risk profile and were thus at a greater risk for heart attack to begin with (this is referred to as *confounding by disease severity*). This result poses the question as to whether the heart attacks occurred because of the drug or whether they were due the subjects' higher baseline risk. Randomization ensures that both groups (those receiving a drug and those receiving a placebo) are balanced with respect to baseline characteristics.

The second advantage of RCTs is *blinding*. Blinding ensures that neither the investigators nor the subjects are aware who receives the drug or placebo. This is essential in reducing bias. These two attributes make RCTs true experimental studies, and have put RCTs on the top of the hierarchy of clinical evidence mainly for **questions of drug efficacy.**

RCTs have numerous drawbacks when it comes to quantifying rare adverse drug events. **For example, it would be unethical to randomize patients to NDMA, a presumed carcinogen**[7]. Second, some exposures (including NDMA) require years of patient follow up to be able to statistically examine the potential risk of the agent with respect to cancer. **Logistically, it is unfeasible to follow tens of thousands of patients' precise exposure to NDMA for years to assess the risk of NDMA with cancer.**

Strengths of RCTs:

- True experiments that minimize bias due to randomization and blinding
- Ideal to examine drug efficacy

Limitations of RCTs:

- Difficult to set up and execute
- Low generalizability to real clinical settings
- Unable to examine safety of drugs or carcinogens due to:
    - Small sample size
    - Short follow up periods
    - Ethical limitations

7.2 Observational Studies

Observational studies are studies where investigators examine a research hypothesis (e.g., NDMA causes cancer) in a large population. The term "observational" is used because exposure is usually fixed (captured through questionnaires or a large database) and is not controlled by the investigators as it is done in RCTs. There are two main types of observational study designs—cohort studies and case-control studies.

Cohort studies follow a group of subjects having similar characteristics and assess the effect of a specific exposure (drug, diet, carcinogen) with respect to a specific outcome (cancer formation). Investigators then quantify the rate of disease in those exposed and unexposed groups and use statistical techniques to control for confounding variables. The strength of the association in cohort studies is usually presented as a relative risk (RR), rate ratio (RR) or a hazard ratio (HR). A number of cohort studies have been published where subjects' exposure to NDMA has been measured and compared to subjects with lower levels of NDMA exposure[25].

Case-control studies are sometimes referred to as "research in reverse" since investigators first identify individuals with a disease of interest (e.g., cancer) and then work backwards by determining exposure prevalence to a chemical or a drug amongst the cases (those with the disease) and controls (those without the disease).

Advantages of Observational Studies:

- Can quantify uncommon outcomes that require long follow ups
- Can include large sample sizes to be able to statistically answer uncommon outcomes

Disadvantages of Observational Studies:

- All clinical variables or their precise measurement might not be known for a particular outcome.
- Some important variables might not be available for adjustment

Because examining the risk of cancer with NDMA requires following large cohorts of subjects (generally tens of thousands) for many years observational studies (either cohort or case-control studies) are the ideal study design to address the question of risk of cancer with NDMA or NDEA.

7.3 Interpreting Magnitude of Effects in Epidemiologic Studies: Relation Between Sample Size and Statistical Significance

Epidemiologic studies present the strength of the evidence (or magnitude of an effect) using different metrics. For case-control studies, the metric is mainly the odds ratio (OR), which demonstrates the ratio of the odds among the cases compared to controls. For cohort studies, several metrics are used, including the relative risk (RR), rate ratio (RR), hazard ratio (HR), and standardized mortality ratios (SMR). Whether these effect measures are statistically significant can be interpreted from the corresponding confidence intervals around these effects. For example, a relative risk or RR of 2.0 in a study examining the effect of a carcinogen with respect to colon cancer with a 95% confidence interval that is between 1.5-4.0 means that the carcinogen increases the risk of colon cancer by a factor of two. The 95% confidence intervals between 1.5 to 4.0 means that if theoretically a study was repeated 100 times, in 95/100, the RR will fall

between 1.5-4.0. Because the lower bound of the confidence interval (1.5) is greater than 1.0, the results are said to be statistically significant. However, in a situation where the RR is 2.0 but the confidence interval included a value that was less than 1.0 (e.g. 0.5-4.0), then it could be inferred that the carcinogen increases the risk by a value of 2.0, but the results are not statistically significant, as the lower bound of the confidence interval also includes 1.00 (no effect). This happens, for the most part, due to a small number of events which is a function of an inadequately small sample size[26]. These results can be interpreted as inconclusive or imprecise, as the RR can be as low as 0.5 (protective) or as high as 4.0 and more likely than not (based on a confidence interval of 0.5-4.0) if the study was repeated, that the RR will be greater than 1.0.

Thus, in studies where the magnitude of the measure of effect (OR, RR, HR) has a wide confidence interval, where this range can fall partly within the range of no effect (lower end) but at the same time the upper end of this value can fall in the clinically meaningful effect (e.g., RR >1.0), then one can not conclude that the results of the study are necessarily negative (i.e., a specific carcinogen does not increase the risk of cancer)[27]. While one could interpret the results as inconclusive, it would be improper to conclude that the carcinogen was not harmful.

8.0 EPIDEMIOLOGIC STUDIES OF NDMA AND CANCER: METHODOLOGY

I undertook a search of the medical literature using standard and accepted methodology[28,29], which includes a systematic search of the literature and accepted *Medical Subject Headings* (**MeSH**) using specific inclusion and exclusion criteria. Published epidemiologic studies that met the inclusion criteria were identified. Studies were reviewed focusing on both strengths and limitations of each study. A detailed search strategy is laid out in section 8.1.

8.1 Search Strategy and Study Ascertainment

To identify the epidemiologic studies in this report I searched the electronic medical database MEDLINE (National Library of Medicines) through the OVID platform from 1946 to April 9, 2021. I included the following search terms:

1. *Dimethylnitrosamine OR Nitrosamines OR Nitrites (which are MeSH terms that include NDMA and NDEA)*
2. *A search was done for all cancers as well as a separate search for the following cancers types: stomach, pancreatic, liver, colon, rectal, kidney, esophageal, breast, bladder, kidney, thyroid, blood, lung, prostate, brain.*
3. *Search 1 and 2 were combined*
4. *Results from the above search were restricted to the following studies: Epidemiologic Studies OR Case-control Studies OR Cohort Studies*

- *A similar search for the above was preformed using Google Scholar. Reference list of retrieved studies was also examined to identify potentially relevant studies that might not have been captured through the MEDLINE and Google Scholar searches.*

8.2 Study Inclusion/Exclusion Criteria

***Study Inclusion Criteria**:*

- Used classic epidemiologic study designs such as case-control, cohort studies, or pooled analysis of the two (meta-analysis) that presented measures of effect such as the odds ratio, relative risk, rate ratio, hazard ratio or standardized mortality ratio to demonstrate the magnitude of the effect of NDMA/NDEA and cancer.
- Clearly defined the type of cancer in each study.
- Clearly defined and quantified nitrosamine compounds (as the main exposure of interest in the study) and risk of cancer. However, more weight was placed on studies that specifically examined exposure to NDMA or NDEA (using a validated approach) and provided measure of effects (RR, OR, HR) through diet or occupational exposure as this is the most optimal approach that would allow examining a potential causal link between NDMA or NDEA use and cancer. Studies that included nitrosamines or nitrites were included as along as they also included NDMA or NDEA in their measure of effect (RR, OR, HR).
- Studies that looked at valsartan containing NDMA or NDEA formulations. These studies had to have been case-control studies, cohort studies, RCTs or meta-analyses. These studies also had to be able to differentiate NDMA or NDEA specific valsartan batches (from valsartan batches that did not contain excessive amounts of NDMA or NDEA).
- Used methodological or statistical techniques to control for confounding variables.

Study Exclusion Criteria:

- **Dietary or occupational studies that did not specifically quantify the amount of nitrosamines or NDMA concentrations. For example, studies of meat intake and cancer where specific levels of NDMA in meat were not quantified.** Moreover, lack of quantifying or categorizing (low vs high) NDMA/NDEA amounts in these studies will make it difficult to necessarily draw a causal link between NDMA/NDEA and cancer. Thus, these studies were reviewed but were not weighted strongly when assessing the risk of cancer with NDMA exposure.

9.0 EPIDEMIOLGOIC STUDIES OF NDMA OR NDEA AND CANCER: RESULTS

A number of published studies have examined the risk of NDMA/NDEA exposure and cancer. These studies can be divided into 1) studies of occupational exposure to NDMA; 2) epidemiologic studies that assessed NDMA or NDEA exposure through diet.

9.1 Occupational Epidemiologic Studies

There are a number of studies that have examined the occupational effects of NDMA/NDEA on the risk of cancer[25,30-32].

The study by *McElvenny*[32] examined a cohort of men working at a rubber and cable manufacturing company, and assessed their risk of death due to respiratory, cardiovascular and cancer related deaths. The study found an increase in mortality of all cancers (standardize mortality ratio (SMR=1.13, 95% CI: 1.11-1.16). Specifically, cancer deaths due to stomach cancer (SMR=1.26, 95% CI: 1.18-1.36), lung cancer (SMR=1.25, 95% CI: 1.21-1.29), and bladder cancer (SMR=1.16, 95% CI: 1.05-1.28) were also elevated. Due to the sample size of the study, other cancers did not demonstrate a statistically significant increase in risk mainly due to small sample sizes. However, the major limitation with this study was that it examined nitrosamine exposure in rubber and cable industry and not necessarily NDMA or NDEA exposure. These men might have been exposed to carcinogens other than NDMA/NDEA. Thus, the specificity of cancer risk that can be specifically allocated to NDMA/NDEA in this study was low.

Another study by *Straif*[30] followed a cohort of 8,933 men who worked in rubber factories and assessed their risk of cancer mortality from different types of cancer (from 1981 to 1991) among higher vs. lower categories of nitrosamine exposures were examined. **An increase in the risk of all cancer deaths was identified** (RR=1.4, 95% CI: 1.0-1.8). However, this study did not control for all potential confounding variables (such as death due to competing cancers), had a shorter follow time and did not have statistical power to capture cancer events by specific organ vs. cancer in general.

The largest occupational study with the longest follow up that has specifically examined NDMA with respect to different types of cancer deaths was a large cohort study by *Hidajat*[25]. This study followed 36,441 males (35 years or older) who were British rubber factory workers for a 49-year period, using a validated approach that quantified different levels of NDMA exposure from rubber dust or fumes. Exposure to NDEA was not captured in this study. The study then quantified the risk of deaths due to different types of cancer and found a statistically significant **increase in the risk of the following cancer deaths: stomach, esophageal, pancreatic, bladder, liver, lung, prostate and blood cancers (lymphoma, leukemia, multiple myeloma)**. The study had several strengths. First, given that cancer formation and progression to eventual death can take years, this study's follow up period was long enough to detect the different types of cancer deaths, notable even rarer types of cancer (e.g., gastrointestinal cancers). Third, the study controlled for death due to non cancer causes[33]. For example, in the analysis that examined the risk of death due to prostate cancer, subjects who died of a heart attack and subsequently were no longer at risk of developing prostate cancer were appropriately controlled for in the analysis. Finally, unlike epidemiologic questionnaire-based studies that examined the risk of NDMA and cancer, quantification of NDMA exposure information was significantly more robust in the study by *Hidajat*[25]. *Hidajat's*[25] NDMA measurement did not rely on subject recall, which can be prone to recall bias and is a limitation of questionnaire-based studies[31].

As with all epidemiologic studies, *Hidajat*[25] had some limitations. While the study did control for the confounding effect of age, it did not directly control for smoking, a variable also associated with cancer. However, the authors acknowledge that simulations using smoking in the data did not change the results. Moreover, an unmeasured confounder—a confounder that could not be measured in the study (e.g., family history of cancer), would need to have a strong effect to change the results for the 10 different cancers reported by *Hidajat*[25]. Below (Table 1). I present the magnitude of the hazard ratios for the 10 different types of cancer presented by *Hidajat*[25]. The last column is the value of the hazard ratios needed to reverse the elevated hazard ratios (presented in the study) for each cancer and take them to null (no effect), which was generated using the E-value methodology[34] a published validated method that can show the change in the hazard ratio needed to reverse the positive findings for a study due to the effect of the unmeasured confounder[34]

Table 1. Magnitude of the hazard ratios (HRs) needed for 10 different types of cancer (column 2) to eliminate the increased risk of cancer (column 1).

Type of cancer	HRs without unmeasured confounder	Magnitude of HR to reverse the risk in column 1
Stomach	1.72	2.8
Pancreatic	2.60	4.6
Esophageal	3.04	5.3
Liver	2.86	5.1
Bladder	2.82	5.0
Prostate	5.36	10.1
Lung	1.70	2.7
Lymphoma	2.25	3.9
Leukemia	3.47	6.4
Myeloma	2.81	5.0

The results of the analysis in Table 1 demonstrate that the magnitude of the effect of an unmeasured confounder has to be large in order to eliminate the risk of the cancers observed by *Hidajat*[2]. Thus, based on these results it is unlikely that unmeasured confounders can reverse the increased risk of the 9 different types of cancer observed by *Hidajat*[25].

9.2 Epidemiologic Dietary Studies

These studies are case-control or cohort studies that have examined the risk of cancer with NDMA or NDEA. My search resulted in 10 case-control studies[35-44] that met the inclusion criteria, 7 cohort studies[45-51], and one meta-analysis[52] that met the inclusion criteria. All the studies assessed the risk of NDMA and different types of cancer. Only one study examined the risk of NDEA, with pancreatic cancer as the endpoint[37]. All these studies examined the risk of NDMA with different categories of NDMA/NDEA exposure mainly comparing subjects among the highest categories to those in the lowest category.

In these studies, NDMA exposure information was usually ascertained through a dietary questionnaire. The risk of cancer among those exposed to the highest levels of NDMA is then

compared to those exposed to the lowest levels. Statistical adjustments were used to adjust or control for potential confounding variables.

10.0 EVIDENCE OF SPECIFIC CANCER TYPES DUE TO NDMA/NDEA EXPOSURE

Below I describe the epidemiological evidence of NDMA/NDEA exposure and different types of cancer.

10.1 Stomach Cancer

Animal studies have shown an increase in the risk gastrointestinal cancer with NDMA exposure[14,16]. With respect to occupational studies, the study by *Straif*[30] demonstrated an increase in the risk of stomach cancer deaths with nitrosamines (HR=1.2, 95% CI: 0.5-3.2), which was not statistically significant. Unlike the study by *Hidajat*[25], *Straif*[30] identified a smaller number of stomach cancer deaths (potentially due to a smaller study sample size), did not control for competing risk bias, and looked at nitrosamines in general and not specifically NDMA or NDEA. *Hidajat*[25] clearly demonstrated an increase in the risk of stomach cancer deaths as NDMA exposure increased (HR=1.72, 95% CI: 1.41-2.10).

Dietary epidemiologic studies have also found an increase in the risk of stomach cancer with NDMA use. Some of these studies have quantified the risk of cancer among different categories. For example, a 1995 study by *La Vecchia*[38] showed that those who took ≥190 (ng/day) of NDMA had a 37% increased risk of developing stomach cancer (OR=1.37, 95% CI: 1.1-1.70) than those taking ≤130 (ng/day) when controlling for a number of potential confounding variables, including family history of stomach cancer[38]. **Of note, the daily NDMA amount in some of the manufactured batches of valsartan are as high as 52,500 ng[53] in one 320mg tablet of valsartan, which would be 276 times higher than the high dose category defined in the *La Vecchia* study[38].**

A large cohort study from Sweden by *Larsson*[51] that followed 61,433 subjects for 18 years also found a statistically significant increase in the risk of stomach cancer after adjusting for important confounders including body mass index (BMI) and alcohol use. The authors found that subjects who were exposed to greater than 194ng/day of NDMA in their diet had a 96% increase (RR=1.96, 95% CI: 1.08-3.58) in the risk of stomach cancer than those taking less than 41ng/day). **Given that the highest NDMA doses identified in some of the valsartan batches is 52,500ng[53], this means that some of the valsartan batches had as much as 270 higher doses of NDMA than the highest NDMA category in Larsson[51].**

A case-control study be *De Stefani*[39] identified 340 cases of gastric cancer and 698 controls in Uruguay. The study controlled for a number of confounding variables such as smoking and alcohol. The study found that those taking NDMA at doses greater than or equal 270ng (**194 times lower than the 52,500ng[53] found in some of the 320mg tablets of valsartan)** per day had 3.62 (OR=3.62, 95% CI: 2.38-5.51) times or 262% increase in risk of gastric cancer compared to those taking 140ng or less per day. One possible limitation of the study was that it did not control for prior history of stomach cancer.

A population-based case-control study from Italy by *Palli*[43] identified 382 gastric cancers and 561 controls. A multivariable adjusted model found a statistically non-significant increase (OR=1.99, 95% CI: 1.00-3.98) in the risk of gastric cancer among those in the highest NDMA exposure category compared to the lowest. The study did not disclose the NDMA dose cut-off in each category or the number of cases exposed to NDMA which might have been too small (compared to the total non NDMA cancer cases) to reach statistical significance.

There have also been studies that found an increase in the risk of gastric cancer but this increase did not reach statistical significance. For example, a cohort study by *Loh*[50] found a slight increase in the risk of gastric cancer that was not statistically significant (RR=1.13, 95% CI: 0.81-1.57). However, given the imprecise estimates of the risk provided by these studies, one cannot exclude the possibility that a risk might exist, and that the statistically insignificant results might have been due to a small sample size resulting in an inadequate number of stomach cancer cases in this study compared to the disproportionally larger number of variables adjusted in the model, which possibly led to imprecise estimates[54,55].

Another study by *Jakszyn*[47] did not find an increase in continuous users of NDMA with respect to gastric caners. The study followed 521,457 subjects for 6.6 years and did not find an increase in the risk of stomach cancer (HR=1.00, 95% CI: 0.7-1.43). A material limitation of this study is that it included mostly older adults but a description of other comorbid conditions (conditions such as heart disease or diabetes) which are extremely common and complex in older study populations, were not provided. Given that the average follow-up time for subjects who developed stomach cancer was only 3.7 years, it is possible that subjects with a higher prevalence of comorbid conditions died as a result of these conditions and did not have the opportunity to develop stomach cancer. This study also did not control for important confounders, such history of stomach cancer.

Keszei[46] undertook a cohort study of approximately 120,853 subjects with an average of 16 years follow up to examine the risk of nitrosamines with gastric cancer. The adjusted risk of gastric cancers with nitrosamine intake among men was elevated by 6% (HR= 1.06; 95% CI: 1.01-1.10) per 100ng/day intake of NDMA for one type of gastric cancer (gastric non-cardia), and a 31% increase in risk for other types (gastric cardia, HR=1.31, 95% CI: 0.95-1.81 in men) although this result did not reach statistical significance. Among women the risk was also not elevated (HR=0.74, 95% CI: 0.51-1.06). The lack of an effect in this study might be explained by potential for misclassification (inaccurate reporting of different food intake by the subjects) of the diet questionnaire used in the study as stated by the authors. Also, the study did not report the number of subjects lost to follow up which would no longer put them at risk of developing gastric cancer and potentially underestimate the true risk of gastric cancer in this study.

Knekt[45] also conducted a cohort study and did not find an increase in the risk of stomach cancer (HR=0.75, 95% CI: 0.37-1.51). However, the study's wide confidence intervals did not exclude a harmful effect of up to 51% as it only had 68 total stomach cancer cases and it is likely that when these numbers were broken down to categorize NDMA to high vs low categories of exposure, the study potentially lost statistical power to adequately assess this risk. Another reason for this lack of association might be due to imprecision of dietary questionnaires for quantifying NDMA

from different food groups. This imprecision might have led to misclassification of the true NDMA effect with respect to cancer and might have led to null results.

A case-control study from France by *Pobel*[35] showed an increase in the risk of gastric cancer with higher NDMA exposure (OR=7.00, 95% CI: 1.85-26.46) which was defined as 290ng/day or more (**180 times lower than the 52,500ng[53] found in some of the 320mg tablets of valsartan**). Although this study did not control previous history of stomach cancer, the large magnitude of this association makes it unlikely that unmeasured confounders would have changed the results of this study to a null association[34].

A 2015 pooled analysis or meta-analysis of 11 epidemiologic studies that examined intake of NDMA and risk of gastric cancer was undertook by *Song*[52]. A meta-analysis is a statistical technique that pools data from multiple studies, some of which have small sample sizes, with the goal of increasing statistical significance and precision around the effect size. *Song* pooled data from 11 studies including eight described here (Pobel[35], La Vecchia[38], De Stefani[39], Palli[43], Knekt,[45], Keszei[46], Jakszyn[47], Larsson[51] and three additional studies that were part of the study by Keszei[46] and might have provided duplicate data. The pooled relative risk of cancer with NDMA from the 11 studies demonstrated a 34% statistically significant increase in the risk of stomach cancer by Song (RR=1.34, 95% CI:1.02-1.76).

The totality of the evidence from dietary epidemiologic studies demonstrate that it is probable an increase in the risk of stomach cancer with high NDMA intake exists. Although dietary epidemiologic studies might be prone to bias, the totality of the evidence is suggestive that the increase in the risk of cancer with NDMA cannot be explained by bias. Results from some of the dietary studies that have shown an increase in risk of cancer with as high as >270 NG/day[39] of NDMA exposure. Of note, this dose is still a fraction (1/194) of the dose of NDMA present (52,500ng[53]) in some of the manufactured batches of valsartan.

10.2 Colorectal Cancer

Epidemiologic studies have been undertaken to see if the increase in the risk of colorectal cancer seen in animals[56] with nitrosamines (similar in structure to NDMA/NDEA) also translates into an increase in the incidence of cancer at the population level.

With respect to occupational study data, the study by *Hidajat*[25] did not examine the risk of colorectal cancer with NDMA exposure. *Straif*[30] did find an increase in risk with nitrosamine exposure and colon cancer deaths. However, due to the limited number of subjects in *Straif*[30], there were not enough events to produce a statistically significant risk (RR=1.5, 95% CI: 0.5-4.7). No risk with rectal cancer deaths (0.80, 95% CI: RR 0.2-3.9) was observed although the wide confidence intervals (due to only 19 deaths due to rectal cancers) including an upper bound of 3.9 does not exclude an increase in risk.

A number of dietary epidemiologic studies that have specifically quantified NDMA have been published. A large epidemiologic case-control study out of Canada was published in 2013 by *Zhu*[36]. The study identified 1,760 cases of colorectal cancer in Canada and compared them to

2,481 controls. After adjusting for important confounders including (age, sex, caloric intake, body mass index (BMI), cigarette smoking status, alcohol consumption, and physical activity, the study found an increase in the odds of colorectal cancer by 42% (OR=1.42, 95% CI: 1.03-1.96) when comparing the highest category of NDMA (2290ng/day) with the lowest category of 30ng/day. Compared to some of the valsartan batches with high NDMA content, even the highest dose category of the study by *Zhu*[36] would be considered 23 times lower than the amount of NDMA in some of the manufactured batches of valsartan (52,500ng[53]/320mg tablet).

Another study by *Knekt*[45] followed subjects in Finland for up to 24 years and found those who were exposed to the highest levels of NDMA were at twice the risk of developing colorectal cancer (RR=2.12, 95% CI: 1.04-4.33) when adjusting for age, sex, smoking, geographic location, and energy intake. The RR of 2.12 can be interpreted as a 112% increase in risk of colorectal cancer in those exposed to the highest NDMA risk compared to those exposed to the lowest category. The study by Knekt[45] did not provide mean NDMA amounts for each of the exposure categories.

A cohort study by *Loh*[50] examined the risk of NDMA and the formation of 9 different types of cancers, including colon cancer. The study did not find an increase in the risk of colon cancer (HR=0.99, 95% CI: 0.83-1.18), although an increase in the risk of rectal cancer was found (HR=1.46, 95% CI: 1.16-1.84). However, *Loh*[50] did not look at the risk of colon cancer with respect to different levels of NDMA (low vs. high), as was done in the studies by *Zhu*[36] and *Knek*t[45], both of which did find an increased risk of colon cancer. Moreover, the authors state that the average intake of NDMA exposure in their study was considered low. Another limitation of the *Loh*[50] study is that it did not control for competing events such as a heart attack or stroke which would prevent a subject from bring diagnosed with cancer and potentially leading to smaller number of cancer events.

Dietary epidemiologic studies that have specifically quantified the amount of NDMA in diet have shown a probable increase in the risk of colorectal cancer among those exposed to higher doses NDMA and NDEA compared with those exposed to lower doses of either carcinogen.

10.3 Pancreatic Cancer

NDMA has been shown to damage DNA of pancreatic cells, which provides a likely mechanism as to why nitrosamines cause pancreatic cancer[57]. Epidemiologic studies have examined the risk of occupational exposure to nitrosamines and pancreatic cancer. One large case-control study of 504 pancreatic cancer cases and 643 controls by *Fritschi*[58] did not find an association between nitrosamines and pancreatic cancer (OR=0.85, 95% CI: 0.50-1.42). However, neither NDMA or NDEA were specifically evaluated in this study. Given that nitrosamines are comprised of compounds other than NDMA and NDEA, many of which might be less potent carcinogens than NDMA and NDEA, and some of which are considered to be potentially non-carcinogenic, the grouping of nitrosamines as a class would have likely diluted the carcinogenic effect incurred as a result of NDMA or NDEA exposure.

The study by *Straif*[30] was underpowered to appropriately examine pancreatic cancer deaths, as the study only identified 15 pancreatic cancer deaths. The risk of death due to pancreatic cancer after NDMA exposure in *Hidajat*[25] was shown to increase by approximately 2.5 times among

those exposed to high intake of NDMA (HR=2.6, 95% CI: 1.94-3.49). *Hidajat's*[25] study was a significantly more powered study compared to *Straif*[30], as Hidajat had a much larger pool of subjects and subsequently a much higher number of pancreatic cancer death cases (328 vs 15). Additionally, Hidajat had an increased follow-up time compared to *Straif*[30]. For these reasons, *Hidajat*[25] was able to detect the increased risk of death due to pancreatic cancer when exposed to high doses of NDMA.

An epidemiologic study by *Zheng*[37] compared the use of NDMA and NDEA exposure through diet by identifying 957 cases of pancreatic cancer and matching them to 938 controls. The study adjusted for important confounders including race, education level, BMI status, alcohol level, history of diabetes, and smoking. The study found a doubling of the risk (OR= 2.28, 95% CI: 1.71-3.04) or percentage wise, a 128% increase in the risk of pancreatic cancer among those exposed to the highest intake of NDEA. The highest level in this study was defined as 120ng/1000Kcal/day vs. the lowest category of 40ng/1000Kcal/day. **This means that some of the valsartan batches that have NDEA levels measured as high as 5,417.9ng[59] (per 320mg table) would have approximately 22 times higher (computed based on a 2000Kcal/day diet) NDEA amount than the highest category measured in the study by *Zheng*[37].**

A 3% increase in the risk pancreatic cancer with NDMA exposure (from plant and animal sources) was also observed but did not reach statistical significance (OR=1.03, 95% CI: 0.78-1.37). However, a 93% statistically significant increase with pancreatic cancer (OR=1.93, 95% CI: 1.42-2.61) was observed when comparing high vs low categories of exposure to NDMA from plant sources. In this study, high category of NDMA was defined as 1000ng/1000Kcal/day of NDMA exposure compared with the lowest category of 280ng/1000Kcal/day. The results of this study are significant in that the 1000Kcal/day ng intake in this study is approximately 26 times less than some of the manufactured batches that have shown to have up to 52,500 ng of NDMA in one tablet[53].

The preponderance of dietary and occupational epidemiologic evidence demonstrates a probable increase in the risk of NDMA and NDEA with pancreatic cancer. The 'high' dose category of exposure in the dietary studies of NDMA/NDEA and pancreatic cancer have shown to be 52 times and 45 times (for NDMA and NDEA respectively) less than the NDMA and NDEA concentrations identified in some of the manufactured batches of valsartan[53,59].

10.4 Head and Neck Cancers – Pharynx, Larynx, and Esophageal

Nitrosamines including NDMA have also been shown to increase the risk of esophageal cancer in animals[17]. Epidemiologic studies have examined the risk of head and neck cancers with NDMA exposure. In a large prospective cohort study by *Loh*[50] 23,363 men and women were enrolled between 1993 and 1997, and were followed until 2008, examined the risk of a number of cancers with exposure to NDMA[50]. The risk of esophageal cancer was found to be increased by a non-statistically significant value of 13% (RR=1.13, 95% CI: 0.77-1.68). The reason for this non-statistically significant finding is probably due to the small number of cases (55) compared to the large number of covariates (9 variables) used to adjust for potential confounding in this study. As such the RR of 1.13, although not statistically significant, had an upper bound (of the

confidence interval) of 1.68, which means a 68% increased risk of esophageal cancer could not be ruled out.

A case-control study by *Rogers*[42] also examined the risk of nitrosamines, and specifically, NDMA exposure, with oral cancers. After adjusting for important confounders, including smoking and alcohol use, there was approximately a two-fold increase in the risk of oral cancers (combination of esophageal and laryngeal and possibly other oral cancer types) with an OR of 1.82 (95% CI: 1.10-3.00) or 82% increase in risk when comparing the risk among those in the highest NDMA exposure category (>179ng/day—276 times lower than the 52,500 ng/320mg[53] tablet identified in some batches of valsartan) compared with those in the lowest category (<60ng/day). The advantage of this study was the relatively large number of cases and adjustment for important confounders including smoking and alcohol use.

The large cohort study by *Keszei*[46] that involved 120,853 subjects over an average of 16 years also looked at the risk of esophageal cancer with NDMA and found an increase in risk of 15% after adjustment for potential confounding variables (HR=1.15, 95% CI: 1.05-1.25). The study's strength was its large sample size and long follow up period necessary for cancer studies. The HR of 1.15 translated into a 15% increase in the risk of squamous esophageal cancer per 100ng/day increase in exposure to NDMA. This risk was slightly higher among women (HR=1.34, 95% CI: 1.04-1.71). The study by *Rogers*[42] also found an 86% increase in the risk of esophageal cancer (OR=1.86, 95% CI: 0.87-3.95) among those exposed to higher doses of NDMA (>179/ng/day-293 times lower than the 52,500 ng/320mg[53] tablet identified in some batches of valsartan) compared with the lowest dose of <60ng/day although due to the small number of cases (52 esophageal cancer cases vs. 155 oral cancer cases) these results did not reach statistical significance.

Occupational epidemiology data has also examined the association between nitrosamines and head/neck cancers. The study by *Straif*[30] showed an increase in risk of approximately five folds (RR=5.1, 95% CI: 1.2-20.6), but did not control for potential confounding variables which is unlikely to reverse this high magnitude of the risk. The study by *Hidajat*[25], which again was better powered (333 esophageal cancer deaths vs 55 in the study by *Loh*[50]) and had an increased follow up period, found a tripling of the risk of esophageal cancer deaths among those exposed to the higher amounts of NDMA compared to the lowest category of NDMA exposure (HR= 3.04, 95% CI: 2.26-4.09). A statistically significant increased risk of laryngeal cancer was not detected (HR=1.39, 95% CI: 0.67-2.90), due to the study only capturing 62 cases of laryngeal cancer. If *Hidajat*[25] had been more well-powered to detect laryngeal cancer (i.e., had more laryngeal cancer events) it is likely that the increased risk would become statistically significant. Finally, the study by *Knekt*[45] also examined the risk of head and neck cancer with high vs low exposure to NDMA. A 37% non statistically significant increase (RR=1.37, 95% CI: 0.50-3.74) in the risk of head and neck cancers were found although the wide confidence intervals and the high value of the upper bound (3.74) is indicative of the imprecision of the study results possibly due to a small number of cases.

Based on the totality of the evidence in occupational and dietary studies it is probable that high exposure to NDMA increases the risk of head and neck cancers.

10.5 Liver Cancer

Animal studies have shown that even a single injection of NDMA can lead to a number of cancers, including liver cancer[14,16,60]. The study by *Straif*[30] only had 9 deaths due to liver cancer and lacked statistical power to examine this question. The study by *Hidajat*[25] clearly demonstrated an increase in the risk of death due to liver cancer (122 deaths vs 9 deaths from *Straif*[30]) after NDMA exposure by approximately 3-fold (HR=2.86, 95% CI: 1.78-4.59) or 186% increase. Data from large epidemiologic studies with respect to liver cancer that specifically quantified the levels of NDMA exposure and had an adequate follow up were not found. To date, the study by *Hidajat*[25] provides the strongest evidence on the risk of liver cancer as it followed subjects for 49 years and was able to show a dose response relation (high vs low).

10.6 *Bladder Cancer*

Bladder cancer is yet another type of cancer that has been linked to exposure to NDMA. In animal studies, nitrosamines[61] and specifically NDMA,[62] have shown to play a critical role in the bladder cancer process. A number of epidemiologic studies have also examined the risk of bladder cancer with NDMA exposure.

A large epidemiologic study from Europe by *Jakszyn*[48] examined the risk of bladder cancer from NDMA exposure. The study followed 481,419 subjects for approximately ten years and assessed the risk of bladder cancer among those exposed to higher levels of NDMA vs. those exposed to lower levels of NDMA found a 12% statistically nonsignificant increased risk of bladder cancer (RR= 1.12, 95% CI: 0.88-1.44) although an increase of up to 44% could not be ruled out. One major limitation of the study was that it did not provide data on potential comorbid conditions of the study subjects at baseline. It is possible that subjects in the NDMA group might have had more comorbid conditions leading to loss to follow up or death due to competing events such as heart disease or diabetes potentially preventing these subjects from developing bladder cancer.

As with most findings in Straif[30], the data on bladder cancer was also inconclusive (RR=1.3, 95% CI: 0.4-5.0) and could not exclude an elevated risk. And yet again, as a result of *Hidajat*[25] being a more well-powered and designed study which included better ascertainment of competing events and the longest follow up of all epidemiologic studies (that have examined the risk of cancer with NDMA), it was able to detect a statistically significant increase in the risk of bladder cancer deaths of approximately three-folds or 182% increase due to NDMA exposure (RR=2.82, 95% CI: 2.16-3.67), while *Straif*[30] was unable to produce statistically significant results.

The increased risk (which not statistically significant) in the dietary studies is consistent with the statistically significant increased risk demonstrated in Hidajat[25]. Based on the totality of the evidence in occupational and dietary studies it is probable that high exposure to NDMA increases the risk of bladder cancer.

10.7 Prostate Cancer

Animal studies have shown that nitrosamines can increase the risk of prostate cancer[63]. The study by *Loh*[50], which recruited 23,363 men and women from 1993 through 1997, and then followed them until 2008, found that the risk of prostate cancer was not statistically associated with NDMA exposure (RR=1.01, 95% CI: 0.90, 1.13). However, *Loh*[50] was not designed to study only prostate cancer (looked at 9 cancers in total) and did not adjust for previous history of prostate cancer, which is significant as prostate cancer is a recurring disease and men who experience a recurrence might die due to prostate cancer and not develop bladder cancer. Also, the study by *Loh*[50] did not categorize NDMA intake to high vs low categories of intake which would be ideal to examine a potential dose-response with NDMA.

Jakszyn[49] did find a 23% increase in the risk of localized prostate cancer when comparing higher NDMA exposure levels to lower NDMA exposure levels, but *Jakszyn*[49] was unable to produce statistically significant results (RR=1.23, 95% CI: 0.99-1.53). However, the study by *Jakszyn*[49], like the study on bladder cancer by the same authors, provided no information on the comorbidity profile of the subjects as subjects with more comorbid conditions (heart disease) could have died prior to developing or being diagnosed with prostate cancer. This potential limitation is accentuated by the long 10-year follow up of the study which does increase the possibility of death due causes other than prostate cancer.

The study by *Straif*[30] showed a doubling of the risk of prostate cancer, but the result was not statistically significant (RR=2.1, 95% CI: 0.7-6.2). Finally, due to the superiority of *Hidajat* as stated above, a statistically significant increased risk of death due to prostate cancer was apparent (HR=5.36, 95% CI: 4.27-6.73) by a factor of 5 or 436% among those exposed to the highest NMDA levels compared to the lowest NDMA exposure group.

The increased risk of prostate cancer (which not statistically significant) in the dietary studies is consistent with the increased risk demonstrated in Hidajat[25]. Based on the totality of the evidence in occupational and dietary studies it is probable that high exposure to NDMA increases the risk of prostate cancer.

10.8 Blood Cancers – Lymphoma, Leukemia, and Multiple Myeloma

Animal studies have shown that NDMA can damage lymphocytes (white blood cells; a key part of body's immune response) and increase the risk of lymphoma[15]. Dietary epidemiologic studies that specifically examined NDMA with respect to blood cancers are not available. The risk of lymphoma and leukemia have also been examined in occupational studies. One epidemiologic study which met this review's inclusion criteria quantified the risk of nitrites, nitrates or nitrosamines (all three combined) as one entity. *Richardson*[41] undertook a case-control study in Germany with 850 cases of blood cancers. Richardson detected a doubling of the risk of lymphoma (OR=2.22, 95% CI: 1.48-3.35) with exposure to nitrites, nitrates or nitrosamines (all three combined). Thus, the study did not provide the specific risk of NDMA on blood cancers however, the study does provide a strong link between nitrosamines (which include NDMA and NDEA) as a class on the risk of blood cancers. The study by *Straif*[30] was underpowered to examine blood cancers as it had 8, 13, 9 for laryngeal, esophageal and pharyngeal cancers respectively. *Hidajat*[25] demonstrated an approximate two-fold increased risk or 125% increase in

risk of lymphoma death after NDMA exposure (HR=2.25, 95% CI: 1.41-3.59). *Hidajat*[30] also found an increased risk of death due to leukemia and multiple myeloma after NDMA exposure (HR=3.47, 95% CI: 2.35-5.13; HR=2.81, 95% CI: 2.17-3.64, respectively).

Based on the preponderance of evidence from dietary and occupational studies it is probable that high exposure to NDMA increases the risk of bladder cancer.

10.9 Lung Cancer

Nitrosamines have been shown to cause tumors in the respiratory tract of animals[56]. A study by *De Stefani*[44] examined the risk of lung cancer among subjects exposed to different levels of NDMA through diet by undertaking a case-control study. *De Stefani*[44] categorized NDMA from diet using validated methodology. The study identified 320 cases of lung cancer and matched them to 320 controls. After adjusting for important confounding variables, including pack-years of smoking and history of lung cancer, subjects with the highest intake of NDMA (≥270 ng/day) were compared to subjects with the lowest intake of NDMA (≤130 ng/day). *De Stefani* found a statistically significant increased risk of lung cancer when the ≥270 ng of NDMA/day group was compared to the ≤130 ng of NDMA/day group (OR=3.14, 95% CI: 1.86-5.29). **Given that some of the batches of valsartan had as high as 52,500ng/day of NDMA, this translates to 194 times higher NDMA content in these batches compared to the highest category measured in the study by *De Stefani*[44].**

Another case-control study from Hawaii by *Goodman*[40] assessed the risk of dietary nitrites and nitrosamines with respect to the risk of lung cancer (336 lung cancer cases vs. 865 controls). The adjusted odds ratio for use of high intake of NDMA (compared with low intake) was elevated in men (OR=3.3, 95% CI: 1.7-6.2, 230% increase) and women (OR=2.7, 95% CI: 1.0-6.9, 170% increase). One limitation of Goodman is that it is unclear how duration of exposure to nitrosamines was assessed. The study by *Loh*[50] did find a small but non-statistically significant increase risk (RR=1.05, 95% CI: 0.88-1.24). However, this study did not control for competing events or events other than cancer (e.g, heart attacks) that could have prevented a study participant to be at risk of developing cancer.

Finally, in *Hidajat*[25], subjects exposed to NDMA in the highest category had an elevated risk of death due to lung cancer when compared to those in the lowest NDMA exposure category (HR=1.70, 95% CI: 1.54-1.87).

Based on the totality of dietary and occupational epidemiologic studies it is probable that high exposure to NDMA increases the risk of lung cancer.

11. EPIDEMIOLOGIC STUDIES OF VALSARTAN CONTAINING NDMA AND CANCER

11.1 Pottegard

A retrospective cohort study from Denmark by *Pottegard*[64]was conducted in 2018 in an attempt to examine the risk of NDMA containing valsartan and different types of cancer. The study followed 5150 subjects who *possibly* took valsartan containing NDMA from January 2012 to

June 2017 (mean follow up of 4.6 years) and compared their risk of cancer to subjects that the investigators *believed* were unlikely to have ingested valsartan containing NDMA (at the time of the study by *Pottegard*[64], the understanding as to the extent and degree of the valsartan contamination was still in its infancy). After adjusting for potential confounding variables, the study did not find an increased risk of cancer in general (HR=1.09, 95% CI: 0.85-1.41), although a 41% increased risk of cancer in general could not be ruled out. *Pottegard*[63] has a number of limitations, some of the most significant are listed below:

- All subjects who possibly ingested NDMA contaminated valsartan were grouped together as the authors looked at the cumulative dose of valsartan (mg of the pill) as the unit of analysis and not the cumulative amount of NDMA (which is the actual exposure of interest). This limitation will undoubtably lead to misclassification of exposure as the varying amounts of NDMA from different batches and manufacturers is not accounted for using this approach since the study's hypothesis was that higher doses of NDMA will cause cancer and not higher doses of valsartan per se. Due to this limitation, one could reasonably anticipate that the study would not produce statistically significant harmful effect of NDMA with cancer and would have missed a possible risk of cancer with valsartan contaminated NDMA.
- The authors did not account for the possibility that a patient could be switched from a non-NDMA containing valsartan to an NDMA containing valsartan during the follow-up period.
- Daily doses of valsartan (80mg, 160mg, 320mg) were utilized in an attempt to quantify NDMA exposure and stratify the results based on cumulative NDMA exposure. The notion that the level of NDMA contamination will increase as the milligram of the valsartan pill increases, is only true when all pills are made from the same contaminated batch of active pharmaceutical ingredients (API). What has been discovered since the publication of *Pottegard*[64] is that batches of API can vary by orders of magnitude on their level of NDMA contamination. As such, an 80mg tablet of valsartan can have substantially higher levels of NDMA in it than a 320mg tablet. These discrepancies can lead to exposure misclassification, resulting in false negatives.
- The upper bound of the confidence intervals for all the 9 cancers were clinically significant with the lowest being 1.73 and the highest 5.9 (Figure 3, *Pottegard* [64]), which do not exclude the possibly of an increase in risk of the 9 cancers with NDMA.
- Competing events such as death due to cardiovascular events which might have led to subjects dropping out of the study early and no longer being at risk of developing cancer were not accounted for in this study.

Unlike the study by *Hidajat*[25], the study by *Pottegard*[64] suffers from inadequate follow up, lack of control for competing events, and misclassification of valsartan tablets that might have had a high NDMA content with those that might have lower amounts. The combination of these factors probably led to false negative results in this study.

11.2 Gomm et al.

Another recent study by *Gomm*[65] from Germany also attempted to examine the risk of cancer with valsartan formulations that had different amounts of NMDA. The study was a cohort study that used health records of 25 million subjects with health insurance. Subjects entered the cohort if they filled one prescription of valsartan from 2012-2017 and were followed to the first incidence of cancer. The study did not find an overall risk of cancer with NDMA use, but a statistically significant increase in risk with liver cancer was found (HR 1.16; 95% CI: 1.03-1.31) but no risk was detected with 9 other cancers. The study had several limitations which I describe below:

- The major limitation of the study was the median follow up of 3 years which is woefully inadequate to detect all cancer formations that would result from NDMA exposure

- The authors implemented up to a two year 'lag' in the study meaning cases in the first two years of follow up were excluded as these cases were probably not considered to be linked to NDMA. However, this means that the true follow up to detect cancer was only one year (3 years total follow up minus 2 years lag) post NDMA use which would not be considered sufficient induction time for all cancers to occur.

- Similar to the *Pottegard*[64] study, the study by *Gomm*[65] could not specifically identify the true NDMA levels of the various valsartan batches, and the dose-response analysis only looked at cumulative dose of valsartan *per se* and not the cumulative NDMA content in the valsartan formulations (mg of pill vs. ng of NDMA in pill).

- The study did not mention how data for 'switchers' or those who switched between high vs. low NDMA formulated valsartan tablets were analyzed and how the risk for these patients was assessed.

- Similar to the *Pottegard*[64] study, competing deaths or deaths that might have occurred prior to cancer diagnosis leading to patients dropping out (and thus and no longer being at risk of developing cancer) was not controlled for.

11. ASSESSING THE CAUSAL RELATION BETWEEN NDMA AND DIFFERENT TYPES OF CANCER USING THE BRADFORD HILL CRITERIA

The science of causation is a complex discipline that is continually evolving. It is virtually impossible to demonstrate with 100% certainty that substance A causes condition B. There is no accepted gold standard to establish causation in science. However, researchers or policy makers often resort to methodologies such as the Bradford Hill criteria (Hill AB) as a guide to better make decisions on whether a particular exposure (e.g. NDMA) can cause a specific outcome (e.g. cancer).

Below I discuss, using the nine criteria suggested by Bradford Hill, as to why NDMA in valsartan can increase the risk of the above cancers. Bradford Hill did not suggest whether any of

the specific criteria carries a higher weight than others with regard to establishing a causal link. Rather, his intent was to show whether the totality of the evidence from the 9 criteria collectively suggest a causal link between a specific exposure with respect to an outcome (Bradford Hill) (Table 2).

I. Temporal Relationship: Temporality is a critical criterion to establish cause and effect. Temporality means that the cause (NDMA exposure in valsartan) precedes the outcome (cancer). In all the studies that assessed the effect of NDMA (dietary or occupational) the effect of NDMA on the 9 different types of aforementioned cancers, NDMA exposure was measured prior to the diagnosis or death due these different cancers. The study by *Hidajat*[25] excluded cancers that occurred early in the study to ensure that, due to the potential long-latency of the disease, the cancers ascertained in the study were caused by exposure to high levels of NDMA (NDMA in valsartan came before the incidence of the cancers). **Thus, this criterion plays a significant role in the presence of a causal link between NDMA/NDEA in valsartan and cancer.**

II. Biologic Plausibility: This criterion examines whether a biologically plausible mechanism for NDMA in valsartan to cause cancer exists. The answer is yes. Multiple regulatory agencies including the IARC has classified NDMA as carcinogenic. This classification has been granted in part due to an abundance of published animal studies that have shown that through a mechanism of genotoxicity, nitrosamines such as NDMA[17] and NDEA[18] can cause different cancers in animals including gastrointestinal cancers such as liver, esophageal[14,16] pancreatic[57], colon[56], bladder cancer[61,62], prostate cancer[63], lung cancer[56] and blood cancer[14]. A number of animal studies have shown that NDMA and NDEA can cause a number of different types of cancer mainly through their genotoxic effects. **Thus, this criterion plays a significant role in the presence of a causal link between NDMA/NDEA in valsartan and cancer.**

III. Analogy: Analogy asks the question as to whether other carcinogens that are similar in chemical structure to NDMA in valsartan can also cause cancer. The answer is yes. Nitrites, which are compounds chemically similar to NDMA considered precursors to NDMA, have also shown to increase the risk of cancer[66]. **Thus, this criterion plays a significant role in the presence of a causal link between NDMA/NDEA in valsartan and cancer.**

IV. Presence of a dose response relation: Presence of a dose-response relation also strengthens the causal argument. Usually, a causal link between a drug or any carcinogen is strengthened by a dose-response relation where a higher dose leads to a higher risk of an outcome, in this case, cancer. The study by ***Hidajat*[25]** has shown a dose response relation with all the 9 cancers deaths (**esophageal, stomach, colon, liver, pancreas, lung, bladder, prostate, blood**) and was the study with the longest follow up, large sample size and appropriate adjustment for important biases such as death due to competing events. Moreover, dietary epidemiologic studies on stomach cancer[35,38,46,52], pancreatic cancer[37] head and neck cancers[46,42] colon caner[36,45], lung cancer[40,44] and blood cancers[41] have also shown a positive dose response relation. The dietary study by *Jakszyn*[49] for prostate cancer and bladder cancer found an increase in the risk of both cancers with higher doses of NDMA, but the results did not reach statistical significance potentially due to small number of events. Data from large epidemiologic studies that specifically examined the effect of prolonged NDMA exposure through diet are not available for liver cancer. **Overall, presence of a dose response mainly driven by *Hidajat*[25] but also present in dietary epidemiologic studies**

play a significant role in demonstrating a causal link between NDMA/NDEA in valsartan and cancer.

The dose response relation with NDMA and cancer has strong implications to the NDMA contained in some batches of valsartan, as some of these batches have been tested to have as high as 288 times higher NMDA content than some of the highest NDMA dose category in published dietary epidemiologic studies of NDMA[38]. Thus, the risk of cancer in subjects exposed to high levels of NDMA in valsartan for potentially long-periods (used for many months), has a high likelihood of increasing the risk of the aforementioned 9 cancers in these individuals.

V. Specificity: This criterion addresses whether the risk of cancer seen with NDMA in valsartan is specific to that event. However, this criterion does not always hold as other carcinogens can also cause cancer. Moreover, NDMA being a toxic substance has shown to also cause non cancer ailments such as cardiovascular disease[67] in addition to cancer. **Thus, the specificity criterion does not play a significant role in demonstrating a causal link between NDMA/NDEA in valsartan and cancer.**

VI. Consistency: This criterion asks whether there is a link or coherence between the basic scientific evidence and epidemiological evidence that draws a causal link between NDMA contained in valsartan and cancer. The answer is yes. There is basic scientific evidence suggesting that NDMA can cause cancer in animals for all 9 types of cancer. Similarly, the evidence from basic scientific studies corroborates findings from epidemiologic studies **(Table 2 and Figure 1)** that also show an increase in the risk of the 9 different types of cancer with prolonged NDMA exposure. **The totality of evidence suggests a high degree of consistency of the data demonstrating a causal link between NDMA/NDEA in valsartan and cancer.**

VII. Strength of the evidence: This criterion addresses the magnitude of the effect size seen in studies that address the effect of NDMA contained in valsartan and cancer. Although the magnitude of the effect has been variable in different studies, statistically significant associations have been shown with different types of cancer deaths with magnitude of the risk between 1.7-5.36. Specifically, the study by *Hidajat*[25] has shown a statistically significant increase in the risk of the following cancer deaths: **stomach** (OR=1.37, 95% CI: 1.1-1.70), **pancreatic** (RR=2.6, 95% CI: 1.94-3.49), **esophageal** (RR=3.04, 95% CI: 2.26- 4.09), **liver** (RR= 2.86, 95% CI: 1.78-4.59), **colon** (OR=1.42, 95% CI 1.03-1.96), **bladder** (RR=2.82, 95% CI: 2.16-3.67), **prostate** (RR=5.36, 95% CI: 4.27-6.73), **lung** (RR=1.70, 95% CI: 1.54-1.87), **lymphoma** (RR=2.25, 95% CI: 1.41-3.59), **leukemia** (RR=3.47, 95% CI: 2.35-5.13), and **multiple myeloma** (RR=2.81, 95% CI: 2.17-3.64). The study by *Zhu*[36] and *Knekt*[45] also showed an increase in colon cancer (RR=1.42, 95% CI: 1.03-1.96), (RR=2.12, 95%CI:1.04-4.33) respectively. The risk of all 9 cancers were also elevated in dietary studies already stated in section IV (presence of dose response) as well as section 9.0 of this report. **The strength of evidence with respect to the risk of cancer with the NDMA/NDEA exposure in valsartan is considered high.**

VIII. Experimental evidence: This criterion examines whether the evidence in question is supported by experimental evidence i.e., a true experiment or a randomized controlled trial where a control group of non-NDMA exposed patients could also be studied to assess their risk of cancer compared with the NDMA exposed group. This criterion does not apply to the NDMA cancer question as a RCT or true experiment cannot be undertaken to answer this question since it is unethical to randomized subjects to NDMA, a known carcinogen. **This criterion does not apply**

to the NDMA/NDEA cancer question and thus this criterion plays a minor role for this causal question.

IX. Coherence: Coherence examines whether there is a link or coherence between basic science and epidemiological evidence. The answer is yes. **All 9 cancers have shown to have a causal link from well designed, large epidemiologic, occupational and basic scientific studies and I consider this criterion to carry a strong weight for the question of whether NDMA contained in valsartan can cause cancer question.**

Table 2. Application of the Bradford Hill criteria to the evidence of prolonged NDMA exposure on different types of cancer.

B. Hill Criteria	Stomach	Colon	Pancreatic	Esophageal	Liver	Bladder	Prostate	Blood	Lung
Temporal relation	✓	✓	✓	✓	✓	✓	✓	✓	✓
Biologic plausibility	✓	✓	✓	✓	✓	✓	✓	✓	✓
Analogy	✓	✓	✓	✓	✓	✓	✓	✓	✓
Dose response^	1.37 (1.1,1.7)	1.42 (1.03,1.9)	2.6 (1.9,3.4)	3.04 (2.2, 4.0)	2.86 (1.7,4.5)	2.82 (2.1,3.6)	5.36 (4.2,6.7)	2.2* (1.4,3.6)	1.70 (1.5,1.8)
Specificity	No**	No	No	No	No	No	No	No	No
Strength of evidence	1.37 (1.1,1.7)	1.42 (1.03,1.9)	2.6 (1.9,3.4)	3.04 (2.2, 4.0)	2.86 (1.7,4.5)	2.82 (2.1,3.6)	5.36 (4.2,6.7)	2.2* (1.4,3.6)	1.70 (1.5,1.8)
Experimental+ evidence	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Coherence	✓	✓	✓	✓	✓	✓	✓	✓	✓
Consistency	✓	✓	✓	✓	✓	✓	✓	✓	✓

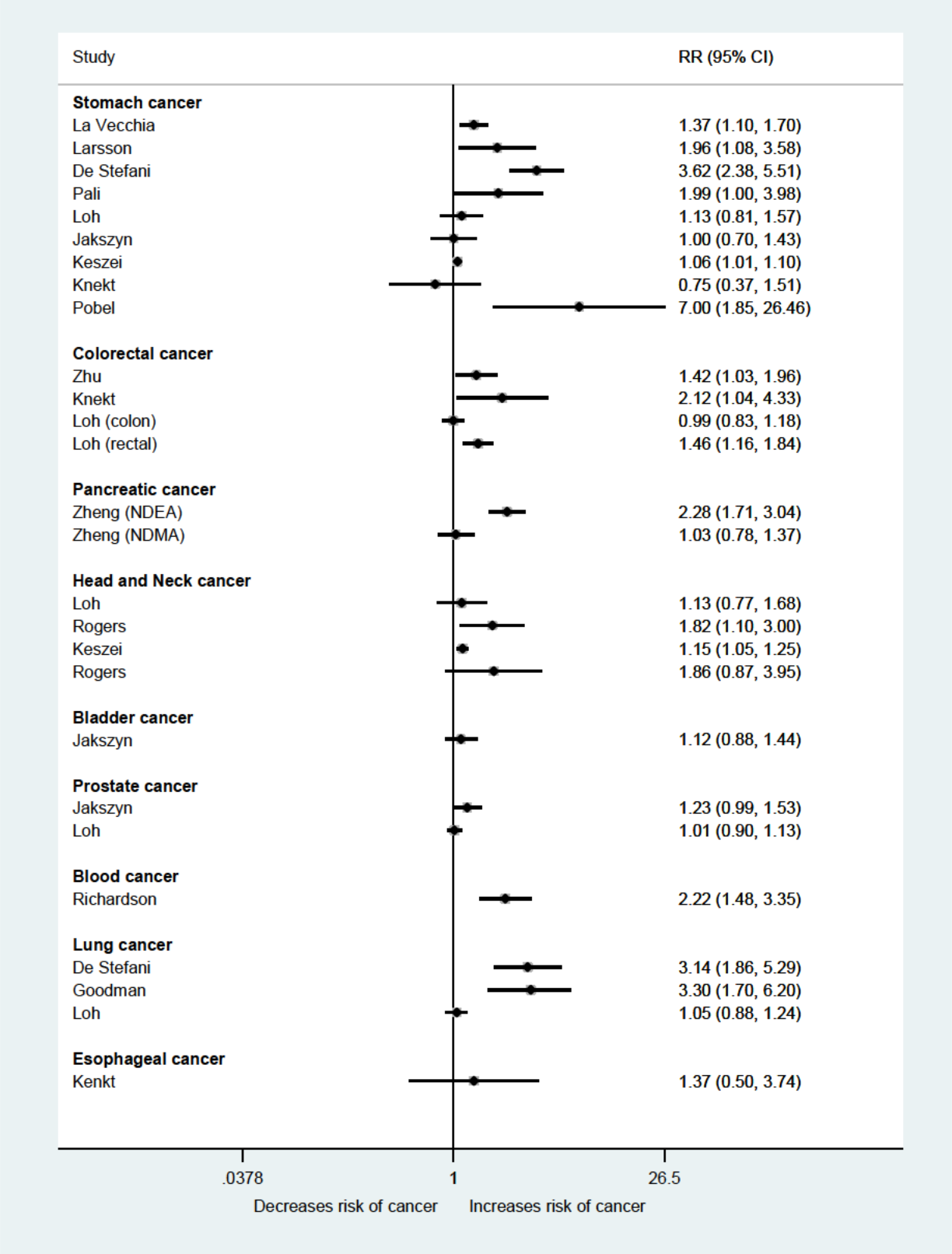
^=Numbers are from the study by Hidajat only as it provides data for a longer-follow up for all cancers. Dose response data for dietary studies are provided in section 9.0 and demonstrate a similar trend.

*=Data for lymphoma only. Results for leukemia and multiple myeloma is similar to lymphoma; N/A= not applicable

**=Since other carcinogens can also cause cancer, the specificity criterion does not apply to the risk of different cancers with NDMA.

+= Experimental evidence refers to randomized controlled trials. None of the studies that examined the risk of cancer with NDMA used the randomized controlled trial design.

Figure 1. Forest plot of dietary studies of NDMA/NDEA with different type of cancers



12. SUMMARY

NDMA, a carcinogen, has shown to cause cancer in animals as well as humans in a number of epidemiologic studies. In 2018, the FDA alerted that some formulations of the drug valsartan contain NDMA concentrations that exceed the daily allowable limit set by the FDA. Chronic exposure to excessive amounts of NDMA in valsartan will put patients who take these drugs for months at a higher risk of cancer. To date, two epidemiologic studies have attempted to quantify the risk of cancer with valsartan formulations that contain excessive amounts of NDMA[64,65]. The results of these studies were inconclusive as they were subject to a number of limitations, mainly a short duration of follow up but most importantly the inability to precisely quantify the amount of NDMA in the valsartan formulations used in both studies.

A number of dietary epidemiologic studies have examined the risk of NDMA/NDEA/nitrosamines on different types of cancer. These studies have mainly examined the risk of cancer with NDMA with different categories of use usually comparing the highest category to the lowest. This is done as it is impossible to identify subjects with absolutely no exposure to NDMA as this agent is ubiquitous in the environment and thus some level of exposure is always expected.

Almost all the studies identified in this review have shown an increase in the risk of NDMA with different types of cancers (with one positive study with NDEA and pancreatic cancer) (**Figure 1**). Some of these studies did show an increase in risk that did not reach statistical significance. The main reason for the non statistically significant results might have been due to a relatively short follow up, differences in the types of questionnaires used, and a small number of total events (sample size) compared to the number of potential confounders adjusted for in the studies which can lead to model overfitting resulting in imprecise results[54,55]. Another potential reason might be due to inadequate cancer latency or the time required for the cancer process to complete and lead to symptomatic disease. Although latency has an important role in the cancer process, it must be noted that cancer latency can have a wide range. In animals, NDMA has shown to cause cancer in as little as 36 weeks[68]. In humans, the antidiabetic drug pioglitazone, a potential carcinogen that acts as a promoter[69] similar to NDMA[14,15] has shown in well designed epidemiologic studies to increase the risk of cancer even after one year of use[70] whereas the latency for other cancers can be longer. Cancer latency can also be individualized and dependent on a multitude of factors including age, genetics, type of drug or carcinogen (as well as dose and duration of use), a person's immune system status among others.

Despite these limitations, many of the dietary epidemiologic studies have shown an increase in the risk of cancer with increasing NDMA exposure. Of note, the amount of NDMA found in some of the valsartan batches (52,500ng in one tablet of valsartan[53]) have shown to be hundreds of times higher than the amounts found in the dietary epidemiologic NDMA studies.

NDEA is also a potent genotoxic carcinogen[18]. Only one epidemiologic dietary study has specifically quantified the risk of NDEA with respect to pancreatic cancer[37] which showed an elevated risk with 120ng/day of use. **Of note, the NDEA content in some of the manufactured**

batches of valsartan has shown to be 45 times higher[59] than the levels used in this study. Moreover, the absence of studies on NDEA and cancer does not mean evidence of absence and given its carcinogenic profile, especially the substantial similarity in the mechanism of action of NDEA in causing cancer to NDMA, it would be expected that NDEA also has the potential to cause the other 8 cancers associated with NDMA.

In the absence of robust epidemiologic studies with long follow ups that can specifically quantify the risk of NDMA containing valsartan and cancer, I can assert that the preponderance of basic scientific evidence, as well as evidence from well-designed occupational and dietary epidemiologic studies with long-follow ups and dose-response analysis, are strongly suggestive of a causal link between NDMA intake and the following cancers: **esophageal, stomach, colon, liver, pancreas, lung, bladder, prostate, and blood (leukemia, lymphoma multiple myeloma). It is my opinion expressed with a reasonable degree of scientific certainty that NDMA in valsartan can cause the preceding 9 cancers.**

13. Addendum

Counsel has asked me to discuss the applicability of the study by *Yoon*[71] as it was raised by a defense witness, Min Li, during deposition testimony. This study would not meet my selection criteria due to its methodologic limitations. I specify these limitations below:

In brief, the study by *Yoon*[71] was a retrospective cohort study from Korea that used large insurance claims databases to examine the risk of cancer with respect ranitidine (a drug that can potentially contain or breakdown *in-vivo* into varying levels of NDMA) compared to the risk of cancer with famotidine (a drug that is not expected to contain or breakdown into NDMA). The study did not find an increase in the risk of cancer generally with ranitidine compared with famotidine (HR=0.99, 95% CI: 0.91-1.07). The study had several limitations which I highlight below:

- The study did not control for switching between the two drugs. For example, if a person took ranitidine for two years and switched to famotidine in the third year and was diagnosed with cancer by the end of year 3, it is not clear to which drug the cancer associated with. The authors do not disclose how the data for such patients were analyzed.

- Competing events other than cancer (e.g., heart attacks) were not adjusted for in this study. For example, if subjects with more severe cardiovascular disease (not controlled for in the study) died early, that subject would no longer be at risk of developing cancer. This might lead to the underestimation of the true risk of ranitidine if a competing events risk analysis is not undertaken. This type of analysis was not undertaken by the authors.

- The authors confirm that the amount of NDMA in the ranitidine tablets was unknown. This is important as the true exposure in this study should be the amount of NDMA content in ranitidine and not ranitidine per se. The study could not identify the ranitidine batches that might have had a higher NDMA content. Thus, without having specific information on the amount of NDMA resulting from the ranitidine tablets used in this study the results of this study are probably false negative results. Thus, one cannot exclude the possibility that high NDMA in ranitidine can increase the risk of cancer.

- The authors identified cancers using the international classification of disease 10th edition coding systems to identify cancers. These codes were used to identify cancers from the Insurance Review and Assessment (HIRA) database in South Korea. The authors do not provide the accuracy of these codes or any validation studies where the accuracy of these codes were examined. It is possible that some cancers might have been misclassified as non cancer conditions (false positives). Cancer registries which have higher accuracies to identify cancers were not used for this study.

- The Following potential confounders which should be controlled for in cancer studies were not were not adjusted for:

    - Alcohol use
    - Overweight
    - History of cancer/genetics
    - Cigarette smoking
    - Cardiovascular disease

In summary, the study by *Yoon*[71] could not answer the question addressed in this report mainly whether high NDMA exposure in a drug (ranitidine or valsartan) can increase the risk of cancer, as the authors could not identify and account for the specific amount of NDMA participants were exposed to over time.

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